REMARKS

Status of the Claims

Claims 1-6, 8-10, 12-16, 20, 21, 36, 49-51, 64, 65, 68-72, 75-77 and 79-99 are in the application.

Claims 9 and 21 are withdrawn from consideration.

Claims 1-6, 8, 10, 12-16, 20, 36, 49-51, 64, 65, 68-72, 75-77 and 79-99 have been rejected.

By way of this amendment, claims 4-6 and 70-72 have been canceled, claims 10, 79, 80, 81, 88 and 91-93 have been amended and new claims 100-111 have been added.

Upon entry of this amendment, claims 1-3, 8-10, 12-16, 20, 21, 36, 49-51, 64, 65, 68, 69, 75-77 and 79-111 will be in the application. Of these claims, claims 9 and 21 remain withdrawn and claims 1-3, 8, 10, 12-16, 20, 36, 49-51, 64, 65, 68, 69, 75-77 and 79-111 remain pending and subject to examination.

Summary of the Amendment

Claims 4-6 and 70-72 have been canceled without prejudice.

Claim 10 has been amended to be a dependent claim which depends from claim 1. In addition, claim 10 has been amended to more clearly state that the individual is identified as having cancer that comprises cancer cells that have a high rate of aerobic glycolysis and are not dependent on endogenously synthesized fatty acid. Support for the amendment of claim 10 is found throughout the claims as originally filed and the specification such as on page 2, lines 13-16 for example.

Claim 79 has been amended to be a dependent claim which depends from claim 1. In addition, claim 79 has been amended to more clearly state that the individual identified as having cancer that comprises cancer cells that have a high rate of aerobic glycolysis have activated Akt or deletion of PTEN. Support for the amendment of claim 79 is found throughout the claims as originally filed and the specification such as Example 2 on page 18 line 24 to page 27 line 9.

Claims 80 and 81 have been amended in view of the amendment of claim 79 to be more clear and consistent with claim 79. Support for the amendment of claims 80 and 81 is found throughout the claims as originally filed and the specification such as Example 2 on page 18 line 24 to page 27 line 9.

Claim 88 has been amended to be more clearly set forth the subject matter of the claim. As amended, claim 88 recites that the therapeutically effective amount of the ATP citrate lyase inhibitor administered to the individual

> is sufficient to inhibit ATP citrate lyase activity in said cancer cells to result in inhibition of conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells, leading to hyperpolarization of mitochondria and increased reactive oxygen species production sufficient to cause said cell to undergo apoptosis.

Support for the amendment of claim 88 is found throughout the claims as originally filed and the specification such as on pages 4 and 5 for example.

Claims 90-92, which are dependent on claim 88, have been amended to more clearly set forth the subject matter of the claims. As amended, claims 90-92 more clearly state that the individual was identified as having cancer that comprises cancer cells that have a high rate of aerobic glycolysis have activated Akt or deletion of PTEN. Support for the amendment of claim 90-92 is found throughout the claims as originally filed and the specification such as Example 2 on page 18, line 24 to page 27, line 9.

New claims 100-111 have been added to more clearly set forth subject matter that corresponds to various embodiments of the invention.

New claim 100 is dependent on claim 88 and refers to embodiments in which

> the individual was identified as having cancer that comprises cancer cells that are not dependent on endogenously synthesized fatty acid and that have a high rate of aerobic glycolysis.

Support for new claim 100 is found throughout the claims as originally filed and the specification such as on page 2, lines 13-16 for example.

New claims 101 and 102 are dependent on claims 89 and 101, respectively, and refer to embodiments in which "the individual was diagnosed as having cancer prior to PET imaging" (new claim 101) and PET imaging that was done "using ^{18}fluoro-deoxyglucose" (new claim 102). Support for new claims 101 and 102 is found throughout the claims as originally filed and the specification such as on page 3, line 25 to page 4, line 2 for example.

New claim 103 is dependent on claim 1 and includes the additional step of "diagnosing the individual as having cancer" and then identifying the cancer as comprising "cancer cells that have a high rate of aerobic glycolysis by PET imaging". Support for new claim 103 is found throughout the claims as originally filed and the specification such as on page 3, lines 19-24 for example.

New claims 104-106 are dependent on new claim 103 and refer to PET imaging using ^{18}fluoro-deoxyglucose (new claim 104), the ATP citrate lyase inhibitor being (-) hydroxycitrate (new claim 105) and the cancer being glioma (new claim 106). Support for new claims 104-106 is found throughout the claims as originally filed and the specification such as on page 3, lines 19 to page 4, line 2, page 9, line 20, and Example 3 for example.

New claim 107 is an independent claims which refers to methods of treating individuals who have been identified as having "cancer that comprises cancer cells that have activated Akt or deletion of PTEN". The claim method comprises the steps of identifying the cancer as having activated Akt or deletion of PTEN, and subsequently administering to a therapeutically effective amount of an ATP citrate lyase inhibitor to the individual. Support for new claim 103 is found throughout the claims as originally filed and the specification such Example 2 on page 18, line 24 to page 27, line 9.

New claim 108 is dependent on new claim 107 and refers to embodiments in which the cancer cells are not dependent on endogenously synthesized fatty acid. Support for new claim 108 is found throughout the claims as originally filed and the specification such as on page 2, lines 13-16 for example.

New claim 109 is dependent on new claim 107 and refers to embodiments in which the ATP citrate lyase inhibitor is administered in conjunction with an anti-cancer antibody. Support

for new claim 109 is found throughout the claims as originally filed and the specification such as on page 12, lines 13-14.

New claim 110 is dependent on new claim 107 and refers to embodiments in which the ATP citrate lyase inhibitor is (-) hydroxycitrate.. Support for new claim 110 is found throughout the claims as originally filed and the specification such as on page 9, line 20 for example..

New claim 111 is dependent on new claim 107 and refers to embodiments in which the cancer is glioma. Support for new claim 111 is found throughout the claims as originally filed and the specification such as in Example 3 for example.

No new matter has been added.

Each of the amended claims and new claims 100-111 read on Invention I set forth in the restriction requirement in the Office Action dated March 21, 2008. Moreover, each of the amended claims and new claims 100-111 read on each of the elected species: i.e. the elected species of cancer cells, Glioblastoma; the elected specific of the ATP citrate lyase inhibitor, hydroxycitrate; and the elected species of tricarboxylate inhibitor, phosphoenolpyruvate.

Claim Rejections – 35 U.S.C. § 103
Kuhajda et al. in view of Schroder et al.

Claims 1-6, 8, 10, 12-15, 20, 50, 51, 64, 65, 68-72, 79-85, and 87-99 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent 5,759,837), in view of Schroder et al. (Int. J. Gynecol. Cancer).

a. Findings and asserted conclusions

The Office's findings on pages 4-6 of the Official Action with respect to Kuhajda are that

> Kuhajda teaches methods of treating carcinomas comprising administering a compound that inhibits fatty acid synthase (FAS), including inhibitors of citrate lyase such as hydroxycitrate.

(Office Action page 4.)

> Kuhajda teaches that since many tumor cells are extremely dependent on endogenous fatty acid

> synthesis, lower FAS activity levels need not exclude a specific tumor as a candidate for therapy with fatty acid synthase inhibitors.

(Office Action page 4.)

> Kuhajda teaches that it is advantageous to combine the active of Kuhajda with chemotherapeutic agents to target rapidly cycling cells.

(Office Action page 4.)

> Kuhajda teaches that the presence of FAS in cells of the carcinoma may be detected by any suitable method, including activity assays, stains, and immunoassays.

(Office Action page 5.) The Office notes that:

> Kuhajda fails to directly teach that the cancer is identified as comprising cancer cells that have a high rate of aerobic glycolysis, that said cancer is identified by PET imaging utilizing 18fluroro-deoxyglucose (18F-FDG), or that said cancer is glioma.

(Office Action page 5.) The Office also notes that

> Kuhajda states that chemotherapy and radiation therapy are the most common forms of tumor treatment.

(Office Action page 6.)

The Office's findings with respect to Schroder are set forth on page 5 of the Official Action which states:

> Schroder teaches the role of 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) in diagnosis of cancer.

(Office Action page 5.)

> Schroder states that the clinical significance and usefulness of PET has been proven for a variety of malignant tumors, and specifically names glioma.

(Office Action page 5.)

> Schroder teaches that "[i]n 1931 Warburg

> demonstrated that malignant tumors are characterized by an elevated aerobic and anaerobic glycolysis.

(Office Action page 5.)

In view of these findings, the Office concludes that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the ^{18}F-FDG PET imaging as taught by Schroder to diagnose a patient with cancer for treatment with the composition of Kuhajda.

(Office Action page 5.) The rationale asserted to support include that

> One would have been motivated to do so since Schroder teaches that ^{18}F-FDG PET imaging is useful in diagnosing malignant cancers, which, according to Warburg as cited by Schroder, necessarily comprises elevated aerobic glycolysis.

(Office Action page 5.) and that

> There would be a reasonable expectation of success in utilizing the diagnostic method of Schroder to diagnose a carcinoma which is to be treated with the composition of Kuhajda since Kuhajda teaches that the carcinoma may be detected by any suitable method.

(Office Action page 5.)

The Office also concludes that

> It would further have been obvious to one of ordinary skill in the art at the time the invention was made to treat a cancer patient with a FAS inhibitor and a different chemotherapeutic agent or radiation therapy to control tumor growth.

(Office Action page 6.) The rationale offered in support of this conclusion is that:

> One would have been motivated to do so because Kuhajda suggest that FAS inhibitors may be utilized in conjunction with other therapeutic programs, wherein Kuhajda states that chemotherapy and radiation therapy are the most common forms of tumor treatment.

(Office Action page 6.)

In addition, the Office dismisses the claims which contain limitations directed to Akt and PTEN, stating

> With regard to the newly added limitations directed to Akt and PTEN, it is noted that Applicant's elected species of cancer is glioma, wherein Applicant identifies that the newly added claims read on the elected species. Therefore, said glioma would have said identified characteristics associated with Akt and PTEN.

(Office Action page 6.)

b. The rejection as applied to claims 4-6 and 70-72

Claims 4-6 and 70-72 have been canceled and the rejection as applied to those claims is moot.

c. No *prima facie* case established

Applicants respectfully disagree and urge that among the findings of the Office, some findings are incorrect or incomplete. Moreover, certain specific relevant facts are omitted. As presented, the Official Action fails to establish that those skilled in the art at the time of the invention would consider the invention *prima facie* obvious. The combination of references does not produce the claimed invention. In addition, the combination of references teaches away from some aspects of the claimed invention. With regard to some aspects, despite the failure to establish that claims are *prima facie* obvious, when the claimed subject matter is fully understood, the evidence of record rebuts any assertion of obviousness.

i. Erroneous/incomplete findings regarding the teaching of Kuhajda

Turning first to the findings with respect to Kuhajda, the Office's statement that

> Kuhajda teaches methods of treating carcinomas comprising administering a compound that inhibits fatty acid synthase (FAS), including inhibitors of citrate lyase such as hydroxycitrate.

(Office Action page 4) is incomplete with regard to exactly what Kuhajda teaches. In particular, Kuhajda states that the invention disclosed therein

> provides a method of treating mammals with carcinoma by inhibiting fatty acid synthesis by the cells of the carcinoma, such that growth of the cells is inhibited in a manner selectively cytotoxic or cytostatic to the cancer cells.

(Kuhajda specification, column 3, lines 57-61) and more specifically that the methods relate to

> administering fatty acid synthase (FAS) inhibitors or inhibitors of other enzymes of the synthetic pathway for fatty acid as cytotoxic chemotherapeutic agents, thereby reducing tumor burden.

(Kuhajda specification, column 3, lines 63-66.) Additionally, Kuhajda states in the section entitled "II. Treatment Based on Inhibition of Fatty Acid Synthesis" that the

> invention provides a method for ameliorating tumor burden in mammals having carcinoma tumor which contains cells that are dependent on endogenously synthesized fatty acid (fatty acid synthesized within the cells).

(Kuhajda specification, column 7, lines 15-19.) Kuhajda states in the section that

> Tumor burden may be reduced in such mammals by administering to the mammal one or more inhibitors that interfere with fatty acid synthesis or utilization. These inhibitors are cytotoxic to tumor cells which express FAS, and administration which results in reduction of fatty acid synthesis and utilization by the tissue and/or reduction of FAS activity in biological fluids of these mammals will reduce tumor burden.

(Kuhajda specification, column 7, lines 21-28.) As noted in the Official Action, Kuhajda notes that citrate lyase is among the enzymes involved in fatty acid synthesis. According to Kuhajda, inhibitors of enzymes involved in fatty acid synthesis are cytotoxic to cancer cells that are dependent on endogenously synthesized fatty acid and this can be used to treat individual with cancer. Kuhajda states that

> Fatty acid synthesis would be reduced or stopped by inhibitors of these enzymes. The result would be deprivation of membrane lipids, which would cause cell death.

(Kuhajda specification, column 11, lines 11-14.)

Kuhajda provides no specifics with respect to dosages of citrate lyase inhibitors. One skilled in the art reading Kuhajda would conclude that the amount of citrate lyase inhibitor used to treat an individual who has a tumor that contains cancer cells that are dependent on endogenously synthesized fatty acid would be a cytostatic or cytotoxic amount such as an amount sufficient to result in "deprivation of membrane lipids which would cause cell death". A full and fair reading of Kuhajda is not simply attaching to use any amount of citrate lyase inhibitors in any regimen or protocol to individuals who have cancer. Rather, Kuhajda specifically discloses the administration of an amount of citrate lyase inhibitors to individuals who have tumors that contain cancer cells that are dependent on endogenously synthesized fatty acids sufficient to induce cytostatic or cytotoxic effect on the cancer cells including effects which cause cell death due to insufficient levels of fatty acid synthesis necessary to sustain the cells.

In stating the content of Kuhajda and what it fairly teaches to one skilled in the art, the Office's summarization was incomplete in that it did not fully set forth the amount of fatty acid synthesis inhibitors to be used. Kuhajda teaches that amount as being an amount to be the amount sufficient to induce cytostatic or cytotoxic effect on the cancer cells that are dependent on endogenously synthesized fatty acids. One skilled in the art reading Kuhajda as a whole at the time of the invention would conclude that the specific amount of compound such as a citrate lyase inhibitor would be administered in a specific amount that would have a cytostatic or cytotoxic effect on the cancer cells that are dependent on endogenously synthesized fatty acids.

It is noteworthy that while Kuhajda teaches that the invention is direct toward treating individuals who have tumors that contain cancer cells that are dependent on endogenously synthesized fatty acid, Kuhajda suggests that it is unnecessary to actually screen patients to determine if their cancer cells are dependent on endogenously synthesized fatty acid, stating:

> Cells that require endogenously synthesized fatty acid are widespread among carcinomas, particularly the most virulent carcinomas. While it is preferred that the presence of FAS be determined prior to treatment, the skilled clinician will recognize that such determination is not always necessary.

> Treatment of a carcinoma patient with an inhibitor of fatty acid synthesis, particularly a FAS inhibitor, which results in reduction of tumor burden demonstrates the presence of FAS in the tumor. Where a carcinoma patient can be successfully treated by the method of this invention, independent determination of FAS may be unnecessary Such empirical treatment of carcinomas of the type usually found to express FAS is also within the contemplation of this invention.

(Kuhajda specification, column 8, lines 32-45.) First, this suggestion does not alter the dosage taught by Kuhajda which would be an amount that would have a cytostatic or cytotoxic effect on the cancer cells that are dependent on endogenously synthesized fatty acids. The suggestion that it is unnecessary to identify the individuals having cancer cells that are dependent on endogenously synthesized fatty acids does not change the doses taught by Kuhajda. Second, without wishing to disparage Kuhajda in any way, Applicants urge that the logic provided by Kuhajda in this passage is itself flawed and those skilled in the art would immediately recognize that the reasoning is based upon invalid premises and unsound arguments. Essentially, Kuhajda is asserting that any and all compounds which inhibit any enzyme involved in fatty acid synthesis can have no other cytostatic or cytotoxic effect on cancer cells including those cancer cells which are not dependent on endogenous fatty acid synthesis. Moreover, the logic of Kuhajda indicates that any and all cells for which any and all compounds which inhibit any enzyme involved in fatty acid synthesis are cytostatic or cytotoxic must be dependent on endogenously synthesized fatty acid. Neither Kuhajda nor any other evidence supports the logic offered in Kuhajda. Studies of cancer and other cells are replete with examples of compounds which are involved in and affect multiple biochemical pathways. Moreover, Kuhajda's lack of any guidance with respect to effective dosages would necessarily lead one skilled in the art to determine dosages of citrate lyase inhibitors that are cytostatic or cytotoxic to cancer cells that are dependent on endogenously synthesized fatty acid. Treatment of an individual with this amount of citrate lyase inhibitor which results in reduction of tumor burden does not prove that the cancer cells are dependent on endogenously synthesized fatty acid. Kuhajda does not teach

treatment of an individual with this amount of citrate lyase inhibitor other than those which are cytostatic or cytotoxic to cancer cells that are dependent on endogenously synthesized fatty acid nor does Kuhajda teach treatment of an individual who has cancer that is known not to be dependent on endogenously synthesized fatty acid.

ii. Omitted finding regarding the teaching of Kuhajda

Also of note, Applicants refer to the passage in Kuhajda which states:

> it is not contemplated that fatty acid synthesis inhibitors will be useful in combination with agents which produce complement-mediated cell damage via the membrane attack complex, whether initiated by antibody or by the alternative pathway for complement activation (Bhakdi, et al. (1983), "Membrane Damage by Complement," Biochim. Biophys. Acta, 737:343:372). Therefore, this invention is not directed to the use of fatty acid synthesis inhibitors in the presence of exogenously supplied agents which activate the complement-dependent membrane attack complex.

(Kuhajda specification, column 8, line 66 to column 9, line 9.) One skilled in the art following the teachings of Kuhajda would be led away from combining any inhibitor of fatty acid synthesis with an antibody based therapeutic.

iii. Erroneous findings regarding Akt and PTEN

Turning to findings with respect to claims which include limitations with respect to Akt and PTEN, Applicants respectfully urge that the Office's findings in view of Applicants' identification of such claims as reading on the elected species glioma, "said glioma would have said identified characteristics associated with Akt and PTEN" is incorrect. Some but not all gliomas have activation of Akt and deletion of PTEN.

Provided herewith are Exhibits A and B which are scientific peer reviewed articles that clearly and unambiguously indicate that some but not all gliomas have the molecular characteristics with respect to Akt and PTEN. Exhibit A is Smith, J.S. et al. (2001) Journal of the National Cancer Institute 93(16):1246-1256. Exhibit B is Hu, X. et al. (2005) Neoplasia 7(4):356-368.

Table 2 on page 1248 of Exhibit A reports that 11 out of 172 gliomas had homozygous deletion of PTEN while 43 out of the 172 gliomas had mutated PTEN. Exhibit A clearly reports that not all gliomas have alterations in PTEN.

The first paragraph of the section entitled "Introduction" in Exhibit B notes that: 1) the activity of AKT is elevated in a majority of examined Glioblastoma multiforme (GBM) gliomas; and 2) approximately 50%-70% of GBMs have PTEN deletion, mutation or loss of PTEN expression. The last sentence in the second paragraph of the section entitled "Introduction" in Exhibit B notes that loss of PTEN function leads to increased AKT activity. Exhibit B clearly reports that not all gliomas have alterations in PTEN and a majority but certainly not all gliomas have activated AKT.

At the time of the invention, one skilled in the art would have known that identification of a cancer as a glioma is not, contrary to the findings of the Office, definitive with respect to the characteristics set forth in the claims with respect to Akt and PTEN. One skilled in the art would have known at the time of the invention that a glioma may or may not have activated Akt and the glioma may or may not have deletion of PTEN. The findings of the Office which indicate that all gliomas have characteristics set forth in the claims with respect to Akt and PTEN is clearly erroneous and would be immediately recognized as such by those skilled in the art at the time of the invention.

d. The rejection as applied to claims 1-3, 8, 10, 12-15, 20 50, 51, 64, 65, 68, 69, 79-85 and 87-99 – combination of references does not yield invention/missing element

Regarding claims 1-3, 8, 10, 12-15, 20 50, 51, 64, 65, 68, 69, 79-85 and 87-99, Applicants respectfully urge that the combination of Kuhajda et al. and Schroder et al. is insufficient to establish that the claimed invention would be *prima facie* obvious to one skilled in the art. While it is true that under the law, the reference need not be directed at solving the same problem as that of the claimed invention, it is also well established that the combination of references must yield the claimed invention in order to be asserted to establish that the claimed invention is *prima facie* obvious.

Applicants note that the claims have been amended so that each of claims 2, 3, 8, 10, 12-15, 20 50, 51, 64, 65, 68, 69, 79-85 and 87-99 directly or indirectly depend from claim 1. A

comparison of claim 1 with the combined disclosures of Kuhajda et al. and Schroder et al. reveals that the combination of Kuhajda et al. and Schroder et al. do not disclose or render obvious every element of claim 1. Claim 1 recites that the therapeutically effective amount of ATP citrate lyase inhibitor is an amount

> sufficient to inhibit ATP citrate lyase activity in said cancer cells to result in inhibition of conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells, leading to hyperpolarization of mitochondria and increased reactive oxygen species production sufficient to cause said cell to undergo apoptosis.

Nothing in the combined disclosures of Kuhajda et al. and Schroder et al. discloses or suggests this limitation as expressly set forth in claim 1. It is well established that in putting forward an assertion that the claimed invention is *prima facie* obvious, every limitation in the claim must be considered and accounted for in the rejection. It is also well established that in making a rejection based upon obviousness, the Office must provide a clear articulation of the reason why the claimed invention would have been obvious. In the instant rejection, the Office has failed to address the above-quoted limitation in the claim. As discussed, above, Kuhajda is directed at treating cancers which are dependent on endogenous fatty acid synthesis by inhibiting fatty acid synthesis in such cancer cells such that the cancer cells die from a lack of fatty acids essential for cells to survive. One skilled in the art would consider the amount of citrate lyase inhibitor to be administered to be an amount sufficient to kill cancer cells that are dependent on endogenous fatty acid synthesis by inhibiting fatty acid synthesis in such cancer cells such that the cancer cells die from a lack of fatty acids essential for cells to survive. One skilled in the art would consider the amount of citrate lyase inhibitor

> sufficient to inhibit ATP citrate lyase activity in said cancer cells to result in inhibition of conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells, leading to hyperpolarization of mitochondria and increased reactive oxygen species production sufficient to cause said cell to undergo apoptosis.

The combination of Kuhajda and Schroder do not teach each limitation of the claims and the combination does not render the claimed invention as a whole obvious. One skilled in the art combining the teachings of Kuhajda and Schroder wouldn't produce the claimed invention. The Office provides no guidance or reasoning to account for or indicate how one skilled in the art would address the missing element to arrive at the claimed invention.

Applicants do not dispute that the Office's assertion that

> the art is not required to teach the same reasoning for adding components as Applicant,

nor does Applicant take issue with the Office's point that

> the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Applicant.

Applicants, however, urge that the combination of reference must still produce the claimed invention. The different purpose and different problem to be solved disclosed in Kuhajda results in a different method which involves administration of citrate lyase inhibitors in amounts sufficient to be cytotoxic in cancer cells dependent on endogenous fatty acid synthesis by starving such cells of fatty acids needed for survival. The combination of Kuhajda and Schroder has not been asserted to produce the claimed invention with respect to each and every limitation, nor has the Office attempted to address the differences.

The Office urges that the "method of Kuhajda in view of Schroder would result in the same patient population receiving the same treatment" as the claimed invention. Applicants urge that there is nothing in the combination of Kuhajda and Schroder that discloses the "same treatment" as the claim invention. When each limitation of the claims is considered, it is clear that the treatment taught by the combination of Kuhajda and Schroder is different.

e. The rejection as applied to claims 10, 12-15, 20, 65, and 69 – additional issues/ reference teaches away from claimed invention

Regarding claims 10, 12-15, 20, 65 and 69, Applicants respectfully urge that the combination of Kuhajda et al. and Schroder et al. is insufficient to establish that the claimed

invention would be *prima facie* obvious to one skilled in the art as noted above, and further because Kuhajda teaches away from the claimed invention. One skilled in the art, reading Kuhajda would not make the claimed invention. It is well established that prior art references must be considered in their entirety and portions that would lead away from the claimed invention are highly relevant in an obviousness analysis.

With respect to claims 10, 12-15, 20, 65 and 69, each claim includes the limitation that "the cancer cells are not dependent on endogenously synthesized fatty acid" and the methods include the step of identifying the cancer as "a cancer that comprises cancer cells that are not dependent on endogenously synthesized fatty acid". Kuhajda teaches that the invention disclosed therein is specifically to treat individuals who have a

> carcinoma tumor which contains cells that are
> dependent on endogenously synthesized fatty acid
> (fatty acid synthesized within the cells).

One skilled in the art reading Kuhajda and considering it in its entirety would not follow its teachings in a method in which the cancer cells are identified as not being dependent on endogenously synthesized fatty acid. Kuhajda teaches that cancer cells that are dependent on endogenously synthesized fatty acid are the target for and susceptible to the treatment described therein. Kuhajda teaches away from treating individuals identified as having cancer that has cancer cells that are not dependent on endogenously synthesized fatty acid.

f. The claimed invention yields more than predictable results

Applicants respectfully urge that although the combination of Kuhajda et al. and Schroder et al. is insufficient to establish that the claimed invention would be *prima facie* obvious to one skilled in the art, even if the references are combined, the resulting methods yields more than predictable results. Accordingly, although the Office has not established that the claimed invention is *prima facie* obvious, the combination of elements as reconstructed by the Office yields results which could not have been predicted based upon the combined disclosures of the cited art.

It is well established that when a combination of familiar steps are used according to known methods the combination is not obvious if it yields more than predictable results. In the

instant application, claims include methods which combine steps to achieve results greater than the results predicted based upon the cited art. Results superior to those results predicted based upon the cited art is a hallmark of non-obviousness.

g. The rejection as applied to claims 2, 3, 12, 13, 89 and 90 – claimed invention yields more than predictable results

The Office has found that

> Kuhajda teaches methods of treating carcinomas comprising administering a compound that inhibits fatty acid synthase (FAS), including inhibitors of citrate lyase such as hydroxycitrate,

and that

> Schroder teaches the role of 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) in diagnosis of cancer,

and

> states that the clinical significance and usefulness of PET has been proven for a variety of malignant tumors, and specifically names glioma

and therefore

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the ^{18}F-FDG PET imaging as taught by Schroder to diagnose a patient with cancer for treatment with the composition of Kuhajda.

Applicants respectfully urge that the instant method involves different steps to produce a new method in view of the differences between the amount of citrate lyase inhibitor administered to the cancer patient according to the teachings of Kuhajda and the amount of citrate lyase inhibitors administered to the cancer patient in the instant invention. Nonetheless, the combination of administration of citrate lyase inhibitors as taught by Kuhajda and the cancer detection using PET imaging as taught by Schroder which the Office asserts renders the invention *prima facie* obvious in fact yields results beyond what would be predicted in view of the references.

According to the Office, Kuhajda teaches the treatment of cancer with citrate lyase inhibitors. The Office urges that the element in Applicants' claims which refers to the use of PET scanning is merely the use of that technology as one of many that can be used to detect cancer. In the context of choosing to combine Schroder with Kuhajda, nothing in Kuhajda discloses any preference of imaging technologies. In fact, each imaging technology has advantages and disadvantages and the Office has provided no reason why one skilled in the art would have selected PET scan imaging over other technologies to detect cancer if the invention is to inhibit fatty acid synthesis as the treatment method once cancer is detected.

The combination of PET scan detection of cancer and inhibition of citrate lyase is particularly useful when the citrate lyase is inhibited at levels sufficient to inhibit conversion of citrate into oxaloacetic and acetyl-CoA such that hyperpolarization of mitochondria occurs together with an increase in reactive oxygen species production sufficient to cause cells to undergo apoptosis. That is, PET scanning provides a more informative diagnostic tool compared to other detection methodologies when used as part of a method involving administration of citrate lyase inhibitors sufficient to block glycolysis such that apoptosis results.

The selection of PET scanning over another known method, when used in combination with citrate lyase inhibition yields more than a predictable result. The use of PET scanning not only detects the tumor but also serves to inform that the tumor is one which will be susceptible to treatment with amounts of citrate lyase sufficient to block glycolysis at a level such that apoptosis results. CT scanning, for example, in combination with treatment with amounts of citrate lyase sufficient to block glycolysis at a level such that apoptosis results would not be as effective as methods using PET scanning because CT scanning will not differentiate tumors that can be effectively treated using amounts of citrate lyase sufficient to block glycolysis at a level such that apoptosis results. When CT scans are used to identify tumors, the chances of determining the effectiveness of treatment is reduced because not all tumors identified using CT scans will be susceptible to induction of apoptosis using citrate lyase inhibitors to inhibit glycolysis.

As noted in the findings, PET scanning detects tumors which have high rates of glycolysis. Also noted in the findings is that citrate lyase can be used as a cytotoxic or cytostatic agent against cells that are dependent on endogenous fatty acid synthesis. In methods in which citrate lyase inhibitors are used to treat cancers that are dependent on endogenous fatty acid synthesis, detection by PET scanning provides no advantages over other cancer detection methods.

Kuhajda discloses using amounts of citrate lyase sufficient to be cytotoxic or cytostatic to cancer cells that are dependent on endogenous fatty acid synthesis while the instant invention uses amounts of citrate lyase inhibitors sufficient to block glycolysis at a level such that apoptosis occurs in cancer that exhibit high rates of glycolysis. These differences make the methods less obvious. Setting aside these differences, however, the claimed invention is more than merely the method disclosed in Kuhajda with the selection of PET scan to yield a predictable result. The use of PET scanning in the claimed method makes the invention more effective and such a result would not be predicted by combining the teachings of Kuhajda and Schroder.

The use of PET scanning compared to other detection methods identifies patients who are particularly good candidates for treatment using amounts of citrate lyase sufficient to block glycolysis at a level such that apoptosis results in cancer that has high rates of glycolysis. The advantages of using PET scanning in combination with amounts of citrate lyase sufficient to block glycolysis at a level such that apoptosis results in cancer that has high rates of glycolysis provides superior and unexpected results which could not be predicted based upon the combination of using PET scanning in combination with amounts of citrate lyase sufficient to be cytotoxic or cytostatic to cancer cells that are dependent on endogenous fatty acid synthesis.

In the instant case, PET scanning provides identification of the intended patient population whereas other imaging technology does not. In the case of Kuhajda, PET scanning provides no advantages over other technologies. Thus, one would predict that the results of combining Kuhajda and PET scanning would yield results comparable to the results of combining Kuhajda and other imaging technology. One would not predict that the results of

combining the dosages taught in the instant invention with PET scanning would yield results superior to the results of combining the dosages taught in the instant invention with other imaging technology.

It is well settled that when considering obviousness of a combination of known elements, the operative question is whether the combination is more than the predictable use of prior art elements according to their established functions. In the instant case, the drug administration element is not identical to that of Kuhajda so it is not "known". Nonetheless, when combined with PET scanning, the claimed administration protocol achieves results which could not be predicted based upon the teachings of Kuhajda. PET scanning selects the patients that have cancer with the specific characteristics targeted by the claimed invention. No such selection is made when following the teachings of Kuhajda and, in stark contrast to the instant invention, any alternative detection step would be expected to work just as well. Yielding results that are not predictable, the claimed invention is clearly not obvious.

h. The rejection as applied to claims 79-85, 87 and 91-93 – additional issues/claimed invention as a whole produces unexpected results

Regarding claims 79-85, 87 and 91-93, Applicants respectfully urge that the combination of Kuhajda et al. and Schroder et al. is insufficient to establish that the claimed invention would be *prima facie* obvious to one skilled in the art as noted above, and further argue that the combination of Kuhajda and Schroder does not render obvious the claims to treating individuals who have cancer which has activated Akt or deletion of PTEN. As noted above, the Office has incorrectly concluded that all gliomas have these molecular traits when in fact it is well established that some but not all gliomas have activated Akt or deletion of PTEN. Accordingly, the dismissal of the claims as obvious as stated in the action was improper.

The subject matter of claims 79-85, 87 and 91-93 is not obvious. As shown in the Examples of the instant application, citrate lyase inhibitors were more effective against cancer cells with activated Akt than they were against cancer cells without activated Akt. Nothing in the combination of Kuhajda and Schroder would have led one skilled in the art to expect this difference in effectiveness of the claimed methods.

It is well settled that unexpected results are evidence of nonobviousness. In the instant case, the greater susceptibility of the claimed administration protocol in cancer with activated Akt or deleted PTEN could not be predicted based upon the teachings of Kuhajda and Schroder. Yielding results that are not predictable, the claimed invention is clearly not obvious.

g. Rejection should be withdrawn

The subject matter of claims 1-3, 8, 10, 12-15, 20, 50, 51, 64, 65, 68, 69, 79-85, and 87-99 is not obvious under 35 U.S.C. 103(a) over Kuhajda et al. in view of Schroder et al. The Office has failed to establish that the claimed invention would be *prima facie* obvious to those skilled in the art at the time of the invention. The combination of Kuhajda et al. and Schroder et al. does not yield the invention as claimed. When the teachings in Kuhajda are fully considered and the facts properly ascertained as to what the disclosure would teach to one skilled in the art, combination of Kuhajda et al. and Schroder et al. clearly does not disclose the effective amount of the citrate lyase inhibitor as set forth in each claim expressly or by way of dependence. In addition to not providing all elements of the claim, the Office has also failed to provide any reasoning or articulation of the rationale underlying the rejection with respect to the differences between the claimed invention and the cited art. Moreover, the results of the present invention could not be predicted from the combined teachings of Kuhajda and Schroder. The present invention has advantages which are neither present in the method produced by the combination of references nor are those advantages predictable based upon the disclosure in the cited references. In addition, Kuhajda clearly teaches away from some claims. Moreover, the data in the specification demonstrate that some populations within the elected species as set forth in the claims are more susceptible to treatment than others. An error in the facts regarding molecular diversity within the elected species by the Office resulted in a failure to appreciate the additional basis for patentability of some claims.

The Office has not established that claims 1-3, 8, 10, 12-15, 20, 50, 51, 64, 65, 68, 69, 79-85, and 87-99 are obvious in view of the combination of Kuhajda et al. and Schroder et al. Applicants respectfully request that the rejection of claims 1-6, 8, 10, 12-15, 20, 50, 51, 64, 65, 68-72, 79-85, and 87-99 under 35 U.S.C. 103(a) as being unpatentable over Kuhajda et al. in

view of Schroder et al., as applied to claims 1-3, 8, 10, 12-15, 20, 50, 51, 64, 65, 68, 69, 79-85, and 87-99 be withdrawn.

Kuhajda et al. in view of Schroder et al. and further in view of Bru et al.

Claims 16, 36, 49 and 75 are rejected under 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent 5,759,837), in view of Schroder et al. (Int. J. Gynecol Cancer) as applied to claims 1-6, 8, 10, 12-15, 20, 50, 51, 64, 65, 68-72, 76, 77, and 79-99 above, and further in view of Bru et al. (U.S. Patent 5,219,846).

a. Findings and asserted conclusions

The findings of Kuhajda and Schroder are discussed above.

The Office notes that

> Kuhajda, while teaching that FAS inhibitors (e.g. ATP lyase inhibitors) can be combined with other chemotherapeutic agents, fails to directly teach that the composition further comprises a tricarboxylate transporter inhibitor, namely phosphoenolpyruvate (elected species).

With respect Bru, the Office notes that

> Bru teaches methods for treating human tumors; particularly tumors that have become resistant to chemotherapy comprising administering an effective amount of phosphoenolpyruvic acid (see Abstract and column 1, lines 41-64).

The Office concludes that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the phosphoenolpyruvic acid of Bru with the citrate lyase inhibitor (e.g. hydroxycitrate) of Kuhajda for additive anti-tumor effects. One would have been motivated to do so since Kuhajda teaches that FAS inhibitors (e.g. ATP lyase inhibitors) can be combined with other chemotherapeutic agents and phosphoenolpyruvic acid as taught by Bru is a chemotherapeutic agent.

Applicants respectfully disagree.

b. No *prima facie* case established – the rejection as applied to claims 16, 36, 49 and 75

As noted above, the combination of Kuhajda and Schroder to not render the subject matter of claim 1 *prima facie* obvious. The combination of Kuhajda and Schroder do not yield the claimed invention. Nothing in Bru makes up for the deficiency in combination of Kuhajda and Schroder. The combination of Kuhajda, Schroder and Bru do not render claims 16, 36, 49 and 75 *prima facie* obvious.

c. The claimed invention yields more than predictable results

As noted above, the results of the present invention could not be predicted from the combined teachings of Kuhajda and Schroder. The combination of Kuhajda and Schroder does not have the advantages of the claimed invention with respect to the cancer detection also serving as a method to identify patients having cancer susceptible to the drug administration step of the claimed invention.. Nothing in Bru makes up for the deficiency in combination of Kuhajda and Schroder. The combination of Kuhajda, Schroder and Bru do not render the methods of claims 16, 36, 49 and 75 predictable.

d. The rejection as applied to claims 16 and 36 – additional issues/ reference teaches away from claimed invention

In addition, as noted above, Kuhajda teaches away from the subject matter of claim 10, from which claims 16 and 36 depend. Kuhajda similarly teaches away from claims 16 and 36 and for this additional reason the combination of Kuhajda, Schroder and Bru do not render claims 16 and 36 *prima facie* obvious.

e. Rejection should be withdrawn

The subject matter of claims 16, 36, 49 and 75 is not obvious under 35 U.S.C. 103(a) over Kuhajda et al. in view of Schroder et al. and further in view of Bru et al.. The Office has failed to establish that the claimed invention would be *prima facie* obvious to those skilled in the art at the time of the invention. The combination of Kuhajda et al. and Schroder et al. and Bru et al. does not yield the invention as claimed. When the teachings in Kuhajda are fully considered and the facts properly ascertained as to what the disclosure would teach to one skilled in the art, the combination of Kuhajda et al. and Schroder et al. and Bru et al. clearly does not disclose the

effective amount of the citrate lyase inhibitor as set forth in the claims by way of their dependence on claim 1. In addition to not providing all elements of the claim, the Office has also failed to provide any reasoning or articulation of the rationale underlying the rejection with respect to the differences between the claimed invention and the cited art. In addition, Kuhajda clearly teaches away from some claims. Moreover, the results of the present invention could not be predicted from the combined teachings of Kuhajda and Schroder. The present invention has advantages which are neither present in the method yielded by combination of references nor are those advantages predictable based upon the disclosure in the cited references.

The Office has not established that claims 16, 36, 49 and 75 are obvious in view of the combination of Kuhajda et al. and Schroder et al. and Bru et al. . Applicants respectfully request that the rejection of claims 16, 36, 49 and 75 under 35 U.S.C. 103(a) as being unpatentable over Kuhajda et al. in view of Schroder et al. in view of Bru et al. be withdrawn.

Kuhajda et al. in view of Schroder et al. and further in view of Brin et al.

Claims 76, 77 and 86 are rejected under 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent 5,759,837), in view of Schroder et al. (Int. J. Gynecol Cancer) as applied to claims 1-6, 8, 10, 12-15, 20, 50, 51, 64, 65, 68-72, 76, 77 and 79-99 above, and further in view of Brin et al. (U.S. Publication Number 2002/0094339).

a. Findings and asserted conclusions

The findings of Kuhajda and Schroder are discussed above.

The Office notes that

> Kuhajda, while teaching that FAS inhibitors (e.g. ATP lyase inhibitors) can be combined with other chemotherapeutic agents, fails to directly teach that the composition further comprises an antibody.

With respect toBrin, the Office notes that

> Brin teaches that chemotherapeutics which are most commonly used include antitumor antibodies, and namely Herceptin (see entire document, for instance, [0024]). It is noted that Herceptin is the only example of an antibody provided in the instant

> specification (see specification, page 12, lines 13-14).

The Office concludes that

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the Herceptin of Brin with the citrate lyase inhibitor (e.g. hydroxycitrate) of Kuhajda for additive anti-tumor effects. One would have been motivated to do so since Kuhajda teaches that FAS inhibitors (e.g. ATP lyase inhibitors) can be combined with other chemotherapeutic agents and Herceptin as taught by Brin is a common chemotherapeutic agent specifically taught as being anti-tumor.

Applicants respectfully disagree.

b. No *prima facie* case established – the rejection as applied to claims 76, 77 and 86

Claims 76, 77 and 86 each refer to the administration of an anti-cancer antibody as part of the claimed invention.

As noted above, the combination of Kuhajda and Schroder do not render the subject matter of claim 1 *prima facie* obvious. Each of claims 76, 77 and 86 indirectly depend from claim 1. The combination of Kuhajda and Schroder do not yield the claimed invention. Nothing in Brin makes up for the deficiency in combination of Kuhajda and Schroder. The combination of Kuhajda, Schroder and Brin does not render claims 76, 77 and 86 *prima facie* obvious.

c. The rejection as applied to claim 76, 77 and 86 – additional issues/ reference teaches away from claimed invention

Finally, Kuhajda teaches away from the specific subject matter set forth in claims 76, 77 and 86. As noted above, Kuhajda which states:

> it is not contemplated that fatty acid synthesis inhibitors will be useful in combination with agents which produce complement-mediated cell damage via the membrane attack complex, whether initiated by antibody or by the alternative pathway for complement activation.

One skilled in the art following the teachings of Kuhajda would be led away from combining any

inhibitor of fatty acid synthesis with an antibody based therapeutic. One skilled in the art reading Kuhajda and considering it in its entirety would modify its teachings by adding an antibody as part of the methods. Kuhajda expressly teaches that the method disclosed therein would not be used in combination with antibodies. Kuhajda teaches away from treating individuals with the compounds disclosed therein in combination with antibodies.

d. The rejection as applied to claim 77 – additional issues/ reference teaches away from claimed invention

Also note above, Kuhajda teaches away from claim 10, from which claim 77 indirectly depends. For the reasons set forth above with respect to claim 10, Kuhajda teaches away from claim 77.

e. The claimed invention yields more than predictable results

As noted above, the results of the present invention could not be predicted from the combined teachings of Kuhajda and Schroder. Nothing in Bru makes up for the deficiency in combination of Kuhajda and Schroder.

f. The rejection as applied to claims 76, 77 and 86 – additional issues/claimed invention as a whole produces unexpected results

The combination of Kuhajda and Schroder does not have the advantages of the claimed invention with respect to the cancer detection also serving as a method to identify patients having cancer susceptible to drug administration step of the claimed invention. The combination of Kuhajda, Schroder and Brin do not results of the methods of claims 76, 77 and 86 predictable.

g. The rejection as applied to claim 86 – additional issues/claimed invention as a whole produces unexpected results

Similarly, as noted above, in evaluating the subject matter of claim 79, from which claim 86 depends, the Office has incorrectly concluded that all gliomas have the molecular traits set forth in claim 79 when in fact it is well established that some but not all gliomas have activated Akt or deletion of PTEN. Accordingly, the conclusion that claim 79 is obvious as stated in the Official Action was improper. The combination of Kuhajda et al. and Schroder et al. is insufficient to establish that the claimed invention set forth in claim 79 and 86 would be

prima facie obvious to one skilled in the art. The combination of Kuhajda and Schroder does not render obvious the claims to treating individuals who have cancer which has activated Akt or deletion of PTEN.

h. Rejection should be withdrawn

The subject matter of claims 76, 77 and 86 is not obvious under 35 U.S.C. 103(a) over Kuhajda et al. in view of Schroder et al. and further in view of Brin et al.. The Office has failed to establish that the claimed invention would be *prima facie* obvious to those skilled in the art at the time of the invention. The combination of Kuhajda et al. and Schroder et al. and Brin et al. does not yield the invention as claimed. When the teachings in Kuhajda are fully considered and the facts properly ascertained as to what the disclosure would teach to one skilled in the art, the combination of Kuhajda et al. and Schroder et al. and Bru et al. clearly does not disclose the effective amount of the citrate lyase inhibitor as set forth in the claims by way of their dependence on claim 1. In addition to not providing all elements of the claim, the Office has also failed to provide any reasoning or articulation of the rationale underlying the rejection with respect to the differences between the claimed invention set forth in each of claims 76, 77 and 86 and the cited art. In addition, Kuhajda clearly teaches away from each of claims 76, 77 and 86; and in the case of claim 77, Kuhajda teaches away from two distinct features of the claimed invention. Moreover, the data in the specification demonstrate that some populations within the elected species as set forth in the claims are more susceptible to treatment than others. The results of the present invention could not be predicted from the combined teachings of Kuhajda and Schroder and nothing in Brin changes the analysis. The present invention has advantages which are neither present in the method yielded by combination of references nor are those advantages predictable based upon the disclosure in the cited references. With regard to claim 86, that claim has two distinct bases in the results it provides which could not have been predicted. An error in the facts regarding molecular diversity within the elected species by the Office resulted in a failure to appreciate the additional basis for patentability of claim 86 among others.

The Office has not established that claims 76, 77 and 86 are obvious in view of the combination of Kuhajda et al. and Schroder et al. and Brin et al. . Applicants respectfully request that the rejection of claims 76, 77 and 86 under 35 U.S.C. 103(a) as being unpatentable over Kuhajda et al. in view of Schroder et al. in view of Brin et al. be withdrawn.

Conclusion

Claims 1-3, 8, 10, 12-16, 20, 36, 49-51, 64, 65, 68, 69, 75-77 and 79-111 are in condition for allowance. Upon finding claims 1-3, 8, 10, 12-16, 20, 36, 49-51, 64, 65, 68, 69, 75-77 and 79-111 allowable, Applicants respectfully request that claims 9 and 21 be rejoined. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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Attachments

Exhibit A: Smith, J.S. et al. (2001) Journal of the National Cancer Institute 93(16);1246-1256.

Exhibit B: Hu, X. et al. (2005) Neoplasia 7(4):356-368.